Fertility Physicians of Northern California
A Professional Corporation

PROVIDING ADVANCED REPRODUCTIVE HEALTH CARE IN A SUPPORTIVE ENVIRONMENT

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5360 Fishers Lane, Room1061
Rockville, MD 20852

RE: Docket No. 97N-484S
Suitability determination for donors of human cellular and tissue-based products.

To Whom It May Concern:

I am writing to you, as an individual, regarding the above proposed regulations, but also having had experience as a past president of the Society for Assisted Reproductive Technology and also as a member of the Executive Committee of RESOLVE, the national infertility association.

I am writing to express my strong opposition and objection to much of what is contained in the above-proposed regulations. I would like to make the following points:

1) In your summary, it is stated that you wish to screen and test the donors of cells and tissue used in those products for risk factors for and clinical evidence of "relevant communicable disease agents and diseases".

At this time, there is no evidence that the oocytes, embryos, or isolated sperm cells used with IVF are vectors of the diseases you have listed in your proposal. There is no evidence that HIV or other infectious diseases are passed during the process of in vitro fertilization and embryo transfer. I am not aware of any specific papers claiming such transmission, and there have not been any cases reported of HIV transmission over 20 years, in millions of cases of IVF around the world. How can such risk, which has a numerator of zero and a denominator well past a million, be considered "relevant".

2) In your summary it is stated that the agency's action would improve protection of public health and increase public confidence in new technologies while permitting significant innovation in keeping regulatory burden to a minimum. In fact, the proposed regulations would do no such thing. There would not be any protection of the public since there is no demonstrated or even theoretical risk, given current knowledge and, indeed, bringing in such regulations would only increase the public's concern over health problems that do not exist. Furthermore, there are almost no data on which to reassure the public about a risk which the FDA would promote by bringing forth the regulations. How does one disprove or disclaim a non-existent risk? Finally, the regulations you have proposed would not be consistent with keeping the regulatory burden to a minimum, but rather would require extensive documentation, record-keeping, and screening of individuals which would bring significant cost to the average patient undergoing in vitro fertilization. The quarantining which you would require by these regulations will significantly increase costs and increase the number of cycles needed to obtain the same pregnancy rate. It can be conservatively estimated that at least twice as many cycles of in vitro fertilization would be required if donor embryos had to be cryopreserved. Since there are currently approximately 7,000 cycles of donor in the country today and the number would have to be doubled at least to account for freezing, this would be an extra 7,000 cycles at an average cost of $15,000 to $20,000. Therefore, a simple calculation shows that the cost of your proposed regulations to the public would be in the range of $100,000,000 to $150,000,000, hardly a minimum burden.

3) There is great excitement today regarding the real potential benefit to society of stem cell research. The National Institutes of Health has promulgated new guidelines to increase the availability of embryos for stem cell research, which offers almost unlimited potential benefit to the American public and people all over the world. The proposed regulations would result in loss of much larger numbers of donor embryos which potentially could be a source of stem cells. The cost to the society of having fewer stem cells on which to perform valuable research is incalculable, but almost certainly very large.

4) I think the FDA has significantly underestimated the emotional and psychologic burden to patients who would have to undergo the use of donor embryos following cryopreservation. Not only does this add six months to each fresh cycle, during which time the patient and the donor both become older, but also creates great difficulties in potentially finding donors, again for more screening, and also in encouraging donors to come forward in the first instance. These regulations will have the net result of reducing the number of women who will donate while dramatically driving up the cost and creating logistical problems. The delay to

women will result in them having oocytes from older donors with lower probability of success.

5) I also find it curious that you have arbitrarily defined the retrieval of oocytes as "manufacture". Certainly, this is a stretch by any definition. It is also difficult to understand how you can claim that germ cells are products. Would you also claim that embryos are *products*? Clearly, this raises interesting political issues which have never met with rational, let alone satisfactory, discussion over several decades in our government or society.

6) In a number of places in the regulations, it states that the FDA will specifically list relevant communicable disease agents as well as specifically describe in a guidance document risk factors and screening information. It is difficult to know how these risk factors will be identified when, in fact, no risk has ever been identified for use of sperm and eggs in the situation under consideration.

7) In the regulations, you state that proposed Section 1271.80 (d) would require retesting of donor at least six months after date of donation of reproductive cells or tissues that can reliably be stored. Given the current success rates with cryopreservation, it can be argued that these tissues cannot reliably be stored, and therefore would not fall under your proposed regulations.

8) I disagree with your statements under IV - Analysis of Economic Impacts, that the private sector will not spend more than $100,000,000 in a given year as a result of these regulations. Given the calculations above, I think the expenditure will clearly exceed $100,000,000, and therefore it would be necessary for the FDA to perform a cost-benefit analysis according to the unfunded mandates requirements.

9) While SART recommends that its clinics perform appropriate infectious disease testing, the proposed regulations would require extensive documentation and undoubtedly on-site validation and review of such documentation. This would add a great deal of expense and almost certainly unnecessary paper work to the processes which are currently taking place.

10) It is not clear to me what recommendations a physician would give to a patient who screens positive for one of these tests with respect to its impact on reproduction since data are not available to tell us what the impact would be, other than the fact that no problems had ever been reported. Therefore, how do we go about counseling our patients?

11) The estimates of your costs for blood work and for a full health history interview are lower than our current practice charges, and I believe lower than the vast majority of practices around the country. In addition, it is not clear where you have identified the cost of a donor oocyte cycle to be $11,868, since most programs in the country would charge significantly more for this. We charge this much for an IVF cycle, or possibly slightly less, but this does not take into account all of the costs identifying donors, preparation for third-party reproduction, the legal documentation, etc. It is also not taken into account the extensive costs associated with tracking donors and trying to find them, talking to them and counseling them about all of these issues, indeed, finding the donors again for the follow-up testing.

12) It is amazing that the only example you have come up with for transmission of disease is a 1982 case, almost 20 years ago, when an unscreened donor was used. Surely, one cannot claim that "the risks of transmitting HPV and HCV through reproductive tissue should be substantially reduced as a result of donor screening", when there has been one case in the past 20 years where the donor had not been screened at all.

13) Your calculations of the average revenues of the ART centers is clearly overestimated. If one assumes an average fresh IVF cycle cost of approximately $10,000 and there are 80,000 cycles performed per year, then the total revenues for the ART cycles is approximately $800 million. Even adding additional fees for cryopreserved cycles and other tests, the total would not be more than approximately $1 billion. Since up to one-third of the cost of the cycle goes for drugs, this reduces the amount to approximately $650 million, and for many programs a large percentage of the revenue goes to a hospital or other facility for the oocyte retrieval fee, meaning that across the country the total revenues are probably in the range of $550 million. This is significantly less than the amount you have estimated which, if an estimated 300 centers with 2/3 having revenues of $2.5 million, this by itself would be $500 million and the last third having revenues of $11.5 million would be another $1.15 billion, for a total of $1.65 billion. Therefore, I believe you have overestimated the revenues by a factor of approximately 3.

14) In the proposed regulations, the FDA claims that infertility patients would be exposed to a disproportionate risk of several life-threatening infectious disease agents if these regulations are not in place. Again, literature data do not document such concern.

15) Under Section V, The Paperwork Reduction Act of 1995, it is stated that the FDA invites comments on whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility. Again, it is not clear to me that in vitro fertilization is, in fact, the "manufacture" of tissue products, and I am not certain that it should be covered under this type of regulation at all. Additionally, there are no data to support any practical utility of these data. Secondly, I believe the accuracy of the estimated burden of the proposed collection of information is extremely low compared to the actual cost.

16) The FDA clearly underestimates the amount of effort required to explain the risk to recipient, obtain consent from the recipient before using the product, and dealing with each patient. These amounts of time would dramatically increase the cost of these regulations. All of the physicians and staff would have to be knowledgeable about regulations to deal with the numerous questions which undoubtedly come in. We have experience with this in California where laws requiring screening of sperm have added significant amounts of time and effort on behalf of all our staff.

17) I believe these proposed regulations constitute FDA interference in the practice of medicine by requiring quarantining of embryos which will decrease our ability as reproductive endocrinologists to take care of our infertility patients.

In summary, I do not believe there is scientific justification regarding the risk of transmission of these diseases from IVF to merit these regulations. Quarantining would dramatically increase the cost to patients, decrease its success rates, decrease the number of embryos available for potential stem cell research, lower pregnancy rates by causing delays in treatment, result in unnecessary death of probably half the pool of embryos created from donor oocytes, and create increased concern without any demonstrable benefit. I would strongly ask you to reconsider these proposed regulations and to eliminate the onerous provisions which you are contemplating.

Respectfully submitted,

DAVID ADAMSON, M.D.

GDA:BjB

c: Joyce Zeitz/ASRM

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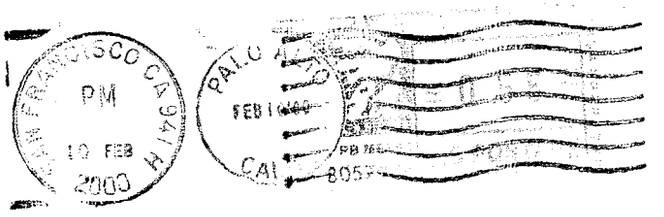

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